Developing an Linear-Parameter Varying Model for Thymocyte Development with Age

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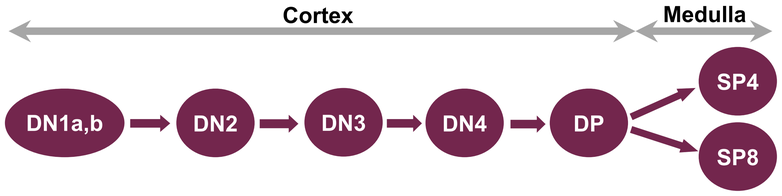
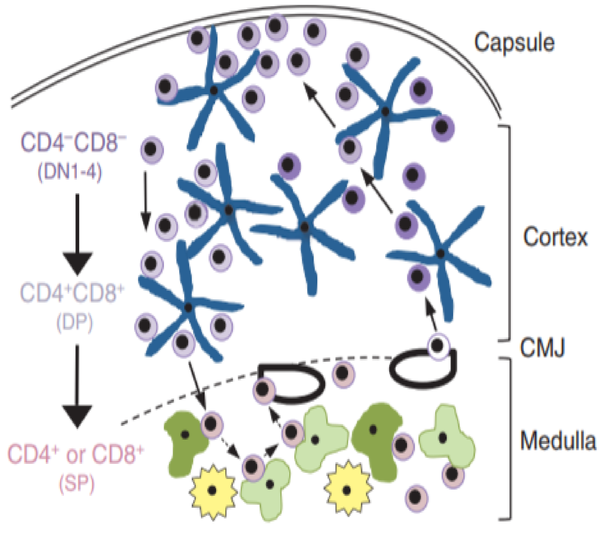
ABSTRACT

T cell progenitors undergo a series of differentiation steps to produce self-tolerant, mature T lymphocytes. We sought to model the impact of thymic epithelial cells (TECs) on thymocyte development in mice across aging. We used thymocyte subset and TEC numbers for male and female mice over 3-18 months of mouse age and developed a linear parameter-varying model with TECs as scheduling variables that control thymocyte development. Our models reflect that TECs have a significant influence on thymocyte development and that thymocyte development is significantly different in male and female mice. Unexpectedly, we observed feedback loops in thymocyte development for both male and female mice. These feedback loops changed with aging consistent with changes that happen in TEC numbers with age. Results from this study could provide new insights into mechanisms controlling thymocyte development and may identify novel approaches to improve thymocyte production with aging.

INTRODUCTION

T cell progenitors migrate to and colonize in thymus. The thymus contains two anatomical compartments, including centrally located medullary regions surrounded by the thymic cortex. T cell progenitors enter the thymus through blood vessels at the border between cortex and medulla and move towards the capsule of the organ, then return and enter the medulla. Cortical and medullary microenvironments along this migratory path direct specific stages of T cell development and promote proliferation and/or cell death. Thymocyte development proceeds through double negative (DN), double positive (DP), and single positive (SP) stages, based on CD4 and CD8 expression; each of these stages is also sub -divided into several discrete steps. The DN and DP stages happen in the cortex, while the SP stages develop in the medulla. The number of thymus and TECs in mice decrease over the age, in a process known as involution.





T cell development in the thymus [1]

[1] Gordon, J. and Manley, N.R., 2011. Mechanisms of thymus organogenesis and morphogenesis. Development, 138(18), pp.3865-3878.

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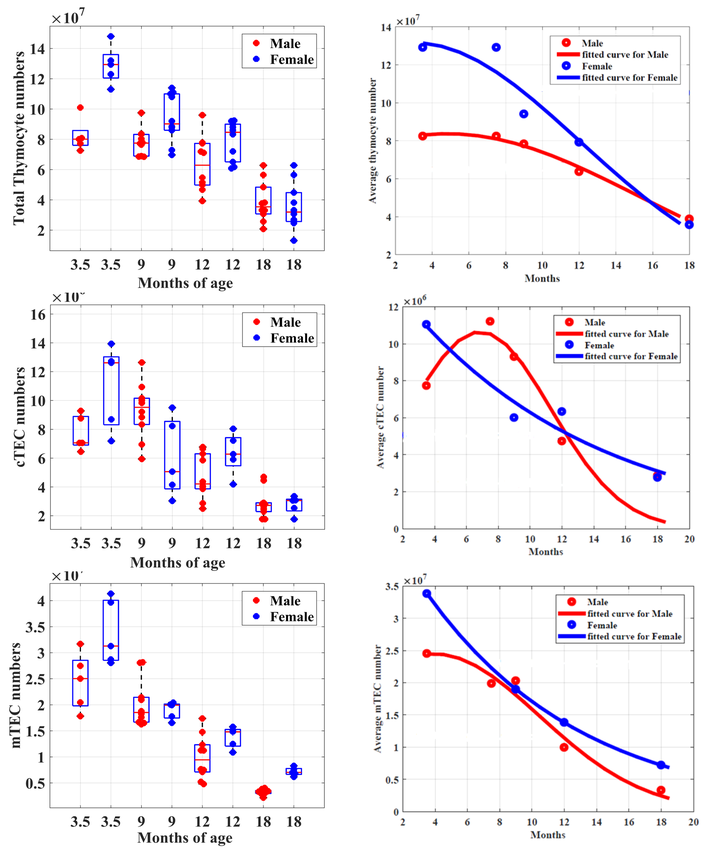
EXPERIMENTAL DATA

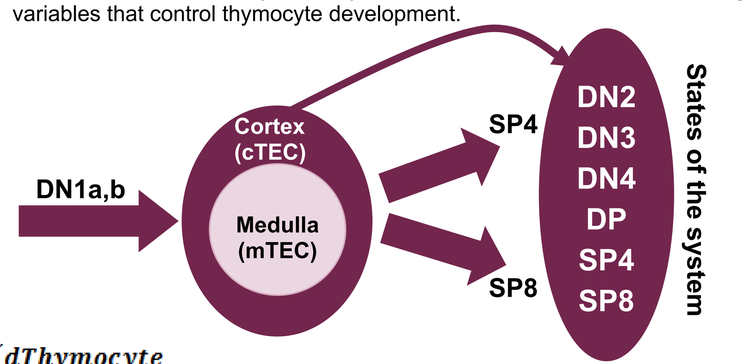
We monitored the number of thymocyte and TEC from experimental data of 3.5 to 18-month-old mice for both male and female. Observations traced decline of the number of thymocyte and TEC with age for both male and female.



The number of thymocytes and TEC decreased consistent with involution in mice. We observed significant differences between the number of thymocytes and TEC of male and female mice. In addition, we observed faster decrease in the number of thymocytes in female compare to male.

METHODS

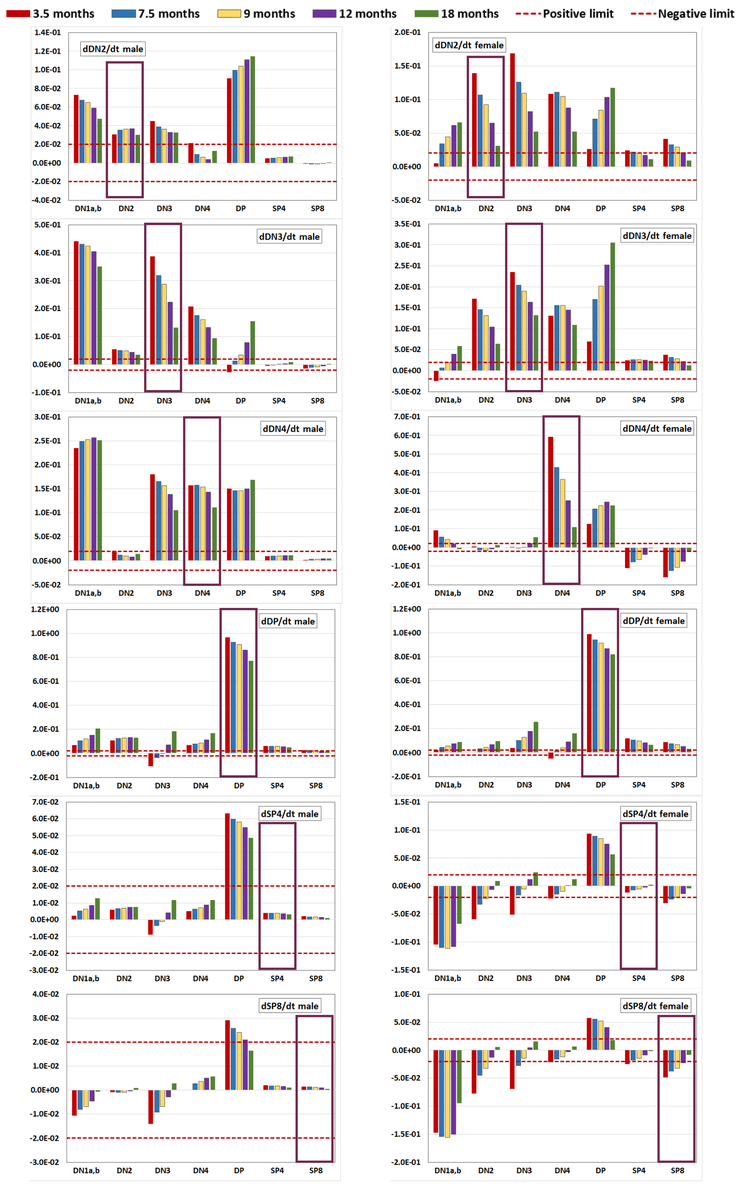
* An LPV system is a linear state-space model whose dynamics vary as a function of certain time-varying parameters called scheduling variables.
* LPV models estimate linear equations for rate of changes of the number of each thymocyte in terms of number of other thymocytes and TEC numbers for male and female mice.
* In this study, we developed an LPV model and considered thymus microenvironment as a dynamic system with TEC numbers as scheduling variables that control thymocyte development.



$$\begin{cases} \dfrac{dThymocyte}{dt} = A(TECs)\,Thymocyte(t) + B(TECs)\,DN1a,b(t) \\ SP = C * Thymocyte(t) \end{cases}$$

RESULTS

We estimated the rate of changes of DN, DP and SP thymocytes with age in terms of TEC numbers for both male and female mice.



We specified each stage with a box and no significant influence with positive and negative limits in the graphs. Positive coefficients subsequent to specified stage illustrate feedback loops in the model for male and female mice. These feedback loops changed with aging consistent with changes that happen in TEC numbers with age. Furthermore, developed models for male and female mice present quite different thymocyte development mechanism.

CONCLUSION

Our model reflect that TEC numbers have a significant influence on thymocyte development. Unexpectedly, we observed feedback loops in thymocyte development for both male and female mice. These feedback loops changed consistent with changes that happen in TEC numbers with age. These results could provide new insights into mechanisms controlling thymocyte development and identify novel approaches to improve thymocyte production with aging.

ACKNOWLEDGEMENT

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